

XENOBIOTIC COMPOUND MODULATED EXPRESSION SYSTEMS
AND USES THEREFOR

ABSTRACT

A novel nuclear receptor, termed the steroid and xenobiotic receptor (SXR), a broad-
5 specificity sensing receptor that is a novel branch of the nuclear receptor superfamily, has been
discovered. SXR forms a heterodimer with RXR that can bind to and induce transcription from
response elements present in steroid-inducible cytochrome P450 genes in response to hundreds
of natural and synthetic compounds with biological activity, including therapeutic steroids as
well as dietary steroids and lipids. Instead of hundreds of receptors, one for each inducing
compound, the invention SXR receptors monitor aggregate levels of inducers to trigger
production of metabolizing enzymes in a coordinated metabolic pathway. Agonists and
antagonists of SXR are administered to subjects to achieve a variety of therapeutic goals
dependent upon modulating metabolism of one or more endogenous steroids or xenobiotics to
establish homeostasis. An assay is provided for identifying steroid drugs that are likely to cause
drug interaction if administered to a subject in therapeutic amounts. Transgenic animals are also
provided which express human SXR, thereby serving as useful models for human response to
various agents which potentially impact P450-dependent metabolic processes. Also provided are
expression systems and expression vectors having SXR receptors and the like operably linked to
target genes of interest.

6 10 14 18 22 26 30 34 38 42 46 50 54 58 62 66 70 74 78 82 86 90 94